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(54) Title: AROMATASE INHIBITORS AND MONOCLONAL ANTI-HER2 ANTIBODIES AS ANTITUMORS AGENTS

(57) Abstract: A method of treating a human being suffering from an hormone-dependent disorder characterized by the overexpression of HER2 comprising administering to said human being an aromatase inhibitor e.g. exemestane, fadrozole, letrozole and anastrozole and an antibody against HER2 e.g. trastuzumab, in amounts effective to produce a superadditive or synergistic therapeutic effect.

aromatase inhibitors and monoclonal anti-her2 antibodies as antitumors agents

The present invention concerns the treatment of hormone dependent disorders characterized by the overexpression of HER2. More specifically, the invention concerns the treatment of a human being susceptible to or diagnosed with a disorder characterized by the overexpression of HER2 with a combination of an anti-HER2 antibody and an aromatase inhibitor.

Proto-oncogens that encode growth factors and growth factors receptors have been identified to play important roles in the pathogenesis of various malignancies, including breast cancer. In particular numerous studies have demonstrated the prognostic relevance of p185(HER2), which is overexpressed in 10% to 40% of human breast tumors. Moreover a recombinant humanized anti-HER2 monoclonal antibody (a humanized version of the murine anti-HER-2 antibody 4D5, referred to as Herceptin®) has been found clinically active in patients with HER2-overexpressing breast cancer (J. Clin. Oncol. 14:737-744, 1996). Also the utility of aromatase inhibitors is well acknowledged in anticancer therapy. However, it is also well known in the art that administration to a patient of therapeutically effective amounts of aromatase inhibitors can cause considerable side effects. The major toxicities are for instance lethargy, hot flashes, rash, transient leukopenia, dizzines, nausea, constipation and vomiting. On the other hand, also administration to a patient of therapeutically effective amounts of an antibody against HER2 can similarly cause considerable side effects, e.g. hypersensitivity, alterations of renal function, myocardial lesions and cardiotoxicity in general.

The inventors of the present invention have found that a combination therapy of an hormone dependent disorder characterized by the overexpression of HER2, comprising a therapeutically effective amount of an aromatase inhibitor and a therapeutically effective amount of an antibody against HER2, can produce a therapeutic effect which is greater than that obtainable by single administration of a therapeutically effective amount of either a sole aromatase inhibitor or a sole antibody against HER2.
Similarly they have found that a combination therapy of an hormone dependent disorder characterized by the overexpression of HER2, comprising a therapeutically sub-effective amount of an aromatase inhibitor and a therapeutically sub-effective amount of an antibody against HER2, can produce substantially the same therapeutic effect, which is obtainable by single administration of a therapeutically effective amount of either an aromatase inhibitor or an antibody against HER2.
The most important, they have found that such newly obtained therapeutic effect is not paralleled by the toxic effects, otherwise caused by single administrations of either therapeutically effective amounts of an aromatase inhibitor or therapeutically effective amounts of an anti-HER2 antibody.
In view of the above, the effectiveness of an aromatase inhibitor and an antibody against HER2 is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the therapeutic effects of the aromatase inhibitor and the antibody against HER2 and thus yields more effective and less toxic treatment for hormone-dependent disorders.

Accordingly, the present invention provides a new and valuable tool in the therapy of hormone dependent

disorders characterized by the overexpression of HER2. The advantages provided by the present invention can be appreciated by their preferred features, described herebelow.

Examples of such disorders are cancers, e.g. breast, cervical, ovarian and endometrial cancers, and endometriosis. However such disorder is preferably breast cancer in a human being, in particular a female.

Accordingly, the present invention provides, as a first object, a pharmaceutical composition comprising an aromatase inhibitor and an antibody against HER2, having a synergistic or superadditive therapeutic activity against an hormone-dependent disorder characterized by the overexpression of HER2.

The present invention also provides the use of an aromatase inhibitor in the manufacture of a pharmaceutical composition for treatment of an hormone-dependent disorder characterized by the overexpression of HER2, the treatment additionally comprising the administration of a composition comprising an antibody against HER2, in amounts effective to produce a superadditive effect.

Examples of aromatase inhibitors according to the invention are exemestane, aminoglutethimide, roglethimide, pyridoglutethimide, anastrazole, trilostane, testolactone, formestane, atamestane, 1-methyl-1,4-androstadiene-3,17-dione (MAD), ketokonazole, fadrozole, letrozole, vorozole and anastrozole.
Preferred examples of aromatase inhibitors according to the invention are exemestane, anastrozole and letrozole, in particular exemestane.

The aromatase inhibitors cited herein are well known products, which are cited for instance in Cancer-Treat-Res.: 94, 231-254, 1998 and WO 99/30708.

Unless otherwise indicated, the terms "HER2" and ErbB2" when used herein refer to the human protein and are used interchangeably.

An antibody against HER2, according to the invention, can be either and "intact" antibody or a fragment thereof.

The term "antibody" is used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity. "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antbody molecules; and multispecific antibodies formed from antibody fragments.

A preferred example of an antibody against HER2 is trastuzumab.

The recombinant humanized monoclonal antibody anti-HER2 trastuzumab (Herceptin®) is described in various scientific publications, for example Cancer Res., 1998, 58: 2825-2831.

The present invention also provides a product comprising an aromatase inhibitor and an antibody against HER2, as combined preparation for simultaneous, separate or sequential administration, in amounts to produce a synergistic or superadditive therapeutic activity against an hormone-dependent disorder characterized by the overexpression of HER2.

In a further aspect, the present invention provides a kit comprising, in a suitable container means, a pharmaceutical composition containing an aromatase inhibitor, as an active agent, and an antibody against HER2, as a further active agent, in amounts to produce a synergistic or superadditive therapeutic activity against hormone-dependent disorder characterized by the overexpression of HER2.

A further aspect of the present invention is to provide a method of treating a human being, particularly a female, suffering from an hormone-dependent disorder characterized by the overexpression of HER2 comprising administering to said human being an aromatase inhibitor and an antibody against HER2, in amounts effective to produce a superadditive or synergistic therapeutic effect.

A still further aspect of the present invention is to provide a method for lowering the side effects (adverse reactions) caused by antitumor therapy with an aromatase inhibitor in a human being, particularly a female, suffering from an hormone-dependent tumor overexpressing HER2, the method comprising administering to said human being a combined preparation comprising an aromatase inhibitor and an antibody against HER2, in amounts effective to produce a superadditive or synergistic antitumor effect.

A still further aspect of the present invention is to provide a method for lowering the side effects (adverse reactions) caused by antitumor therapy with an antibody against HER2 in a human being, particularly a female, suffering from an hormone-dependent tumor overexpressing HER2, the method comprising administering to said human being a combined preparation comprising an antibody

against HER2 and an aromatase inhibitor, in amounts effective to produce a superadditive or synergistic antitumor effect.

By the term "a superadditive or synergistic antitumor effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, by administering a combination of an aromatase inhibitor, as defined above, and an antibody against a HER2, to a human being, particularly a human female. Said preparation having therefore a potentiated antitumor (superadditive) activity with respect to products containing either an aromatase inhibitor or an antibody against HER2.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and oral administration.

By "parenteral" is meant intravenous, subcutaneous, intradermal or intramuscular administration.

Oral administration includes administering the costituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like.

Parenteral administration includes administering the constituents of the combined preparation by subcutaneous, subcutaneous, intravenous or intramuscular injections.

The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the aromatase inhibitor being utilized, the particular pharmaceutical formulation of the antibody against the growth factor receptor being utilized, the particular cancer being treated and the particular patient

being treated.

The dosage ranges for the administration of the combined preparation may vary with the age, condition and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

In the combined method of treatment according to the subject invention, the aromatase inhibitor may be administered simultaneously with the antibody against HER2 or the compounds may be administered sequentially, in either order.

An effective amount of an aromatase inhibitor antitumor agent may vary from about 0.5 to about 500 mg pro dose 1-2 times a day. Exemestane, for example, may be administered orally in a dosage range varying from about 5 to about 200 mg, and particularly, from about 10 to about 25 mg, or parenterally from about 50 to about 500 mg, in particular from about 100 to about 250 mg.

Fadrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

Letrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2.5 mg.

Formestane, for example, may be administered parenterally in a dosage range varying from about 250 to about 500 mg, and particularly, from about 250 to about 300 mg.

Anastrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

In the method of the subject invention, for example for the administration of the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 50 to about 500 mg/m^2 of body surface area.

The therapy method according to the present invention is, in particular, suitable for treating a human being suffering from hormone dependent disorders, characterized by the overexpression of HER2. Typical examples of such disorders are endometriosis and tumors, like ovarian, cervical and endometrial cancers in a human female or breast cancer in a human being, in particular a female.

More in particular, the combined use of an aromatase inhibitor, according to the invention, preferably exemestane, and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, can be suitable for the treatment of patients with cancers over-expressing the HER2 protein, for example, for patient with breast cancer, in particular with metastatic breast cancer, over-expressing the HER2 protein.

Suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy which are obvious to those skilled in the art are within the scope of this invention.

A pharmaceutically composition containing an aromatase inhibitor and/or an antibody against HER2 can be prepared according to well known techniques to those skilled in the art. For instance a pharmaceutical composition containing exemestane can be prepared according to US 4,808,616.

CLAIMS

1. Use of an aromatase inhibitor in the manufacture of a pharmaceutical composition for treatment of an hormone-dependent disorder characterized by the overexpression of HER2, the treatment additionally comprising the administration of a composition comprising an antibody against HER2, in amounts effective to produce a superadditive effect.

2. Use, according to claim 1, wherein the disorder is breast, cervical, ovarian and endometrial cancers, and endometriosis.

3. Use, according to claim 2, wherein the disorder is breast cancer.

4. Use, according to claim 1, wherein the aromatase inhibitor is selected from exemestane, aminoglutethimide, roglethimide, pyridoglutethimide, anastrazole, trilostane, testolactone, formestane, atamestane, 1-methyl-1,4-androstadiene-3,17-dione (MAD), ketokonazole, fadrozole, letrozole, vorozole and anastrozole.

5. Use, according to claim 1, wherein the aromatase inhibitor is exemestane.

6. Use, according to claim 1, wherein the antibody against HER2 is trastuzumab.

7. Use, according to claim 3, wherein the aromatase inhibitor is exemestane and the antibody against HER2 is trastuzumab.

8. A method of treating a human being suffering from an hormone-dependent disorder characterized by the overexpression of HER2 comprising administering to said human being an aromatase inhibitor and an antibody against HER2, in amounts effective to produce a superadditive or synergistic therapeutic effect.

9. A method for lowering the side effects caused by antitumor therapy with an aromatase inhibitor in a human being suffering from an hormone-dependent tumor overexpressing HER2, the method comprising administering to said human being a combined preparation comprising an aromatase inhibitor and an antibody against HER2, in amounts effective to produce a superadditive or synergistic antitumor effect.

10. A method for lowering the side effects caused by antitumor therapy with an antibody against HER2 in a human being suffering from an hormone-dependent tumor overexpressing HER2, the method comprising administering to said human being a combined preparation comprising an antibody against HER2 and an aromatase inhibitor, in amounts effective to produce a superadditive or synergistic antitumor effect.

11. A method according to claim 8, wherein the disorder is breast, cervical, ovarian and endometrial cancers, and endometriosis.

12. A method according to claim 8, wherein the disorder is breast cancer.

13. A method according to claim 8, wherein the aromatase inhibitor is selected from exemestane, aminoglutethimide, roglethimide, pyridoglutethimide,

anastrazole, trilostane, testolactone, formestane, atamestane, 1-methyl-1,4-androstadiene-3,17-dione (MAD), ketokonazole, fadrozole, letrozole, vorozole and anastrozole.

14. A method according to claim 8, wherein the aromatase inhibitor is exemestane.

15. A method according to claim 8, wherein the antibody against HER2 is trastuzumab.

16. A method according to claim 8, wherein the aromatase inhibitor is exemestane and the antibody against HER2 is trastuzumab.

INTERNATIONAL SEARCH REPORT

Interna - Application No
PCT/EP 01/04468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/395 A61K31/5685 A61K31/4196 A61P35/00
//(A61K39/395,31:5685),(A61K39/395,31:4196)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 31140 A (GENENTECH INC) 24 June 1999 (1999-06-24) page 1, line 19 -page 4, line 19 page 11, line 22-25 page 24, line 14-36; claims 1-19	1-16
Y	ALBANELL J ET AL: "Tratuzumab, a humanized anti-HER2 monoclonal antibody, for the treatment of breast cancer" DRUGS OF TODAY / MEDICAMENTOS DE ACTUALIDAD, J.R. PROUS SS.A. INTERNATIONAL PUBLISHERS, ES, vol. 35, no. 12, 1999, pages 931-946, XP000916613 ISSN: 0025-7656 page 938, column 2, line 1 -page 949, column 2, paragraph 1	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interna _ Application No
PCT/EP 01/04468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GREM J L ET AL: "A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ONCOLOGY (CANCER CLINICAL TRIALS), RAVEN PRESS LTD., NEW YORK NY, US, vol. 11, no. 5, 1988, pages 528-534, XP000929348 ISSN: 0277-3732 abstract page 533, column 2, last paragraph	1-16
Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; April 2000 (2000-04) KAUFMANN MANFRED ET AL: "Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: Results of a phase III randomized double-blind trial." Database accession no. PREV200000207045 XP002176335 abstract & JOURNAL OF CLINICAL ONCOLOGY, vol. 18, no. 7, April 2000 (2000-04), pages 1399-1411, ISSN: 0732-183X	1-16
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/EP 01/04468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9931140 A	24-06-1999	AU 1908199 A	05-07-1999
		CN 1281468 T	24-01-2001
		EP 1037926 A	27-09-2000
		NO 20002957 A	11-08-2000
		TR 200001689 T	22-01-2001